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Martindale, The Extra Pharmacopoeia, 28th Edition, pages 10-12, references 2055-f to 2058-h and page 27, references 2098-w and 2099-e.

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(54) Weight control in human and non-human animals

(57) Weight control after a weight loss is achieved by administering (pseudo)ephedrine or ephedrine or an acid addition salt thereof, usually in the form of an orally administerable solid composition. The weight loss may be achieved by administering phenyl propanolamine hydrochloride.

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This print takes account of replacement documents submitted after the date of filing to enable the application to comply with the formal requirements of the Patents Rules 1982.

SPECIFICATION

Weight Control in Humans and Non-human Animals

The invention relates to weight control in humans and non-human animals and is in particular concerned with the use of ephedrine and pseudo-ephedrine (referred to herein as (pseudo)ephedrine), and their acid addition salts for this purpose.

Weight control and weight reduction is an extremely widely practiced excercise. It is usually undertaken for essentially cosmetic réasons, although it is recognized that it has significant health benefits except in cases of marginal excess weight. As personal standards of living having increased, the problem of obesity in varying degrees has become more widespread and, stimulated by demand for remedial treatment, enormous research efforts have been undertaken over recent years.

There are four main approaches to treatment for weight reduction, each of which is commonly combined with dieting and/or exercise. One approach is to administer bulking agents of low or zero caloric value such as methylcellulose or guar gum. On ingestion, these swell in the subjects' stomach to produce a sensation of satiety which achieves appetite suppression. A second approach achieves appetite suppression by chemical action on the central nervous system (CNS) of the patient. Various pharmaceuticals are known for this purpose including amphetamines, fenfluramine, phentermine and diethylpropion. Phenylpropanolamine hydrochloride (PPA) is a modern appetite suppressant which has CNS-activity. Both these methods are effective by reducing food energy intake so that the metabolic processes need to draw on energy potential stored in the body as excess fat. A third approach to weight reduction is the administration of a pharmaceutical which stimulates the mitochondria in brown fat (adipose tissue) to combust body fat and so reduce weight. Ephedrine, (1R, 2S)-2-methylamino-1-phenylpropan-1-ol and its hydrochloride, (αS, βR)-Nα-dimethyl-β-hydroxyphenethylammonium chloride are known to have such an effect (both these materials are specified and characterized in BP and BPC), as is noradrenaline. A fourth approach to weight loss is to produce a general increase in metabolic rate by use of a stimulant such as caffeine. PPA (which herein is to be understood as referring to the amine and to its acid addition salts) is also thought to have this effect as well as its appetite suppressant CNS-activity, although preparations combining PPA and caffeine are in fact known.

All these approaches have well known disadvantages. Bulking agents need to be taken in reasonably large dosage amounts to be effective and this is somewhat unpleasant, especially in the long term. CNS-activity drugs have no apparent suppressant effect after administration has ceased, and are not advisably taken over long periods due to possible term effects and the tendency to addiction in the case of, for example, amphetamines. Adipose stimulators are also not permanent in their effects once administration ceases and there are disadvantageous side effects to the use of ephedrine and to the metabolic combustion of excess fats. Ephedrine (in common with many of the other drugs mentioned above) is a regulated drug available on presciption only. Stimulators such as caffeine can cause side effects such as irritability and long term stimulation at the required levels is medically inadvisable and, in any event, not the most effect means to achieving weight reduction.

Pseudoephedrine, (αR, βR)-β-hydroxy-α-methylphenethyl-N-methylammonium chloride in the hydrochloride acid addition salt form, has now been found to have a stimulant effect on brown fat and which results in combustion of caloric materials such as sugars contained in the bloodstream. In this way, an accomplished weight target in humans (and non-human animals) can be maintained by combusting food energy in the bloodstream and so preventing conversion to stored energy in the form of fatty body deposits. The known use of pseudoephedrine as a nasal decongestant indicates it may be used with safety in the long term without deleterious physiological effects and addiction. Administration can be oral and does not involve the unpleasantness of large dosages as required in the case of bulking agents. There is litte CNS-activity, no general metabolic stimulation (e.g. no secretion of adrenalin) and no combustion of energy stored as fatty deposits.

According to the invention, a method of weight control applicable to human and to non-human animal subjects comprises treating the subject to effect a weight loss and thereafter administering to the subject, usually orally, (pseudo)ephedrine or an acid addition salt thereof (e.g. a hydrochloride) to prevent conversion of intaken food (e.g.) conversion of caloric bloodstream substances) to fatty materials.

The treatment to effect weight loss may conveniently be any of the weight loss treatments referred to earlier. Most advantageously, weight loss treatment will be by administration, usually orally, of a pharmaceutically-active substance which suppresses appetite through CNS-activity. For example, weight loss may be achieved by oral or other administration of PPA, for example a composition containing PPA and a metabolism stimulant such as caffeine.

The (pseudo)ephedrine or salt will usually be administered as a solid formulation, typically tablets, containing the active ingredient together with one or more excipients, for example, lactose, stearic acid, starch or a stearate such as magnesium stearate.

The preferred active ingredient for use in the invention is pseudoephedrine; ephedrine has more side effects.

The (pseudo)ephedrine or salt will normally be provided in unit dosage form, preferably a form comprising 10 to 50 mg of the active substance. Preferred unit dosage is less than 40 mg, especially 10 to 35 mg such as 15 to 30 mg. A typical unit

dosage will be 15 mg or 30 mg administered to human subjects at four hour intervals orally, normally with or just following a normal meal. A 30 mg dose for adults taken before food is also effective. The invention includes within its scope (pseudo)ephedrine or an acid addition salt thereof in unit dosage form, usually in combination with a carrier, such as described above.

Although preferably administration of (pseudo)ephedrine (or salt) forms part of a treatment regime including a previous weight reduction treatment (e.g. with PPA), it may be administered to subjects requiring no weight reduction treatment but who require to avoid weight gain so as to avoid excessive weight and possible eventual obesity, i.e. giving up smoking.

The following specific Example is intended to illustrate the invention:

Example

The following ingredients were admixed in the stated amounts:

	Parts by weight
Pseudoephedrine hydrochloride BP	30
Povidone BPC	4.4
Lactose BP	160
Maize starch BP	20.5
Stearic acid BPC	5
Magnesium stearate BP	2.5

The mixture was then granulated on addition of sufficient industrial methylated spirit.

The granulated mixture was then tableted to produce uncoated 9.5 mm diameter tablets each containing 30 mg of pseudoephedrine hydrochloride.

Administration of the tablets one with a normal meal four times daily for four weeks was found to prevent weight increase in human subjects who had previously lost weight under PPA treatment. On cessation of tablet administration, the subjects increased weight significantly over a period of the same length on identical diets. Administration of the tablets after food without dieting failed to achieve a weight loss but was found to prevent further significant weight increase. Taken before food an appetite suppressant effect is reported.

It is believed that pseudoephedrine does not achieve fat combustion through mitochondric stimulation. It burns off blood sugar. Starvation of blood sugar to the body causes it to start digesting the fat store. The end products of fat burning are ketones which are rather toxic in large quantities, causing ketosis (headaches, nausea, vertigo, vomiting, fatigue, sleep-coma), but to achieve this overdosing would have to be maintained and massive.

In accordance with the invention, pseudoephedrine (many of the embodiments referred to) may be replaced by ephedrine, norephedrine or other substance which stimulates the milochondria to cause combustion of blood sugar (or other caloric substance) and thus prevent conversion to body fat deposits.

CLAIMS

1. A physiologically active dietary composition in unit dosage form for use in weight control applicable to human and non-human animals, the composition comprising, as active ingredient, pseudoephedrine or ephedrine or an acid addition salt thereof and preferably an excipient, the unit dosage of the composition containing 10 to 50 mg of said active ingredient.

2. A composition as claimed in claim 1 wherein the amount of the active ingredient in the unit dosage is 15 to 30 mg.

3. A method of weight control applicable to human and non-human animal subjects which comprises treating the subject to effect weight loss and administering to the subject (pseudo)ephedrine or an acid addition salt thereof to prevent conversion of caloric bloodstream substances to fatty materials.

4. A method as claimed in Claim 3 wherein treatment to effect weight loss is treatment comprising administration of phenylpropanolamine hydrochloride.

5. A composition substantially as hereinbefore described in the foregoing specific Example.

6. A method as claimed in Claim 3 and substantially as hereinbefore described in the specific Example.

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